SEQUENCE LISTING

<110> SHONE, Clifford Charles SUTTON, John Mark HALLIS, Bassam SILMAN, Nigel

<120> Delivery of Superoxide Dismutase to Neuronal Cells

<130> 1581.0800000

<140> 09/831,050

<141> 1999-11-05

<150> PCT/GB99/03699

<151> 1998-11-05

<160> 11

<170> PatentIn Ver. 2.1

<210> 1

<211> 204

<212> PRT

<213> Bacillus caldotenax

<400> 1

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Pro His Ile Asp Lys Glu Thr Met Asn Ile His His Thr Lys His His 20 25 30

Asn Thr Tyr Val Thr Asn Leu Asn Ala Ala Leu Glu Gly His Pro Asp 35 40 45

Leu Gln Asn Lys Ser Leu Glu Glu Leu Leu Ser Asn Leu Glu Ala Leu 50 55 60

Pro Glu Ser Ile Arg Thr Ala Val Arg Asn Asn Gly Gly Gly His Ala 65 70 75 80

Asn His Ser Leu Phe Trp Thr Ile Leu Ser Pro Asn Gly Gly Glu 85 90 95

Pro Thr Gly Glu Leu Ala Glu Ala Ile Asn Lys Lys Phe Gly Ser Phe 100 105 110

Thr Ala Phe Lys Asp Glu Phe Ser Lys Ala Ala Ala Gly Arg Phe Gly 115 120 125

Ser Gly Trp Ala Trp Leu Val Val Asn Asn Gly Glu Leu Glu Ile Thr 130 135 140

Ser Thr Pro Asn Gln Asp Ser Pro Ile Met Glu Gly Lys Thr Pro Ile 145 150 155 160

Leu Gly Leu Asp Val Trp Glu His Ala Tyr Tyr Leu Lys Tyr Gln Asn 165 170 175

Arg Arg Pro Glu Tyr Ile Ala Ala Phe Trp Asn Ile Val Asn Trp Asp 180 185 190 -2-

Glu Val Ala Lys Arg Tyr Ser Glu Ala Lys Ala Lys 195 200

<210> 2

<211> 204

<212> PRT

<213> Bacillus stearothermophilus

<400> 2

Met Pro Phe Glu Leu Pro Ala Leu Pro Tyr Pro Tyr Asp Ala Leu Glu
1 5 10 15

Pro His Ile Asp Lys Glu Thr Met Asn Ile His His Thr Lys His His 20 25 30

Asn Thr Tyr Val Thr Asn Leu Asn Ala Ala Leu Glu Gly His Pro Asp $35 \hspace{1cm} 40 \hspace{1cm} 45$

Leu Gln Asn Lys Ser Leu Glu Glu Leu Leu Ser Asn Leu Glu Ala Leu 50 55 . 60

Pro Glu Ser Ile Arg Thr Ala Val Arg Asn Asn Gly Gly His Ala 65 70 75 80

Asn His Ser Leu Phe Trp Thr Ile Leu Ser Pro Asn Gly Gly Glu 85 90 95

Thr Ala Phe Lys Asp Glu Phe Ser Lys Ala Ala Ala Gly Arg Phe Gly 115 120 125

Ser Gly Trp Ala Trp Leu Val Val Asn Asn Gly Glu Leu Glu Ile Thr 130 140

Ser Thr Pro Asn Gln Asp Ser Pro Ile Met Glu Gly Lys Thr Pro Ile 145 150 155 160

Leu Gly Leu Asp Val Trp Glu His Ala Tyr Tyr Leu Lys Tyr Gln Asn 165 170 175

Arg Arg Pro Glu Tyr Ile Ala Ala Phe Trp Asn Val Val Asn Trp Asp 180 185 190

Glu Val Ala Lys Arg Tyr Ser Glu Ala Lys Ala Lys 195 200

<210> 3

<211> 1067

<212> PRT

<213> Artificial Sequence

~22**0**\

<223> Description of Artificial Sequence:construct

<400> 3

Met Pro Phe Glu Leu Pro Ala Leu Pro Tyr Pro Tyr Asp Ala Leu Glu 1 5 10 15

Pro His Ile Asp Lys Glu Thr Met Asn Ile His His Thr Lys His His 20 25 30





Asn Thr Tyr Val Thr Asn Leu Asn Ala Ala Leu Glu Gly His Pro Asp 40 Leu Gln Asn Lys Ser Leu Glu Glu Leu Leu Ser Asn Leu Glu Ala Leu Pro Glu Ser Ile Arg Thr Ala Val Arg Asn Asn Gly Gly His Ala Asn His Ser Leu Phe Trp Thr Ile Leu Ser Pro Asn Gly Gly Glu Pro Thr Gly Glu Leu Ala Asp Ala Ile Asn Lys Lys Phe Gly Ser Phe 105 Thr Ala Phe Lys Asp Glu Phe Ser Lys Ala Ala Ala Gly Arg Phe Gly Ser Gly Trp Ala Trp Leu Val Val Asn Asn Gly Glu Leu Glu Ile Thr 135 Ser Thr Pro Asn Gln Asp Ser Pro Ile Met Glu Gly Lys Thr Pro Ile 145 Leu Gly Leu Asp Val Trp Glu His Ala Tyr Tyr Leu Lys Tyr Gln Asn 170 Arg Arg Pro Glu Tyr Ile Ala Ala Phe Trp Asn Val Val Asn Trp Asp Glu Val Ala Lys Arg Tyr Ser Glu Ala Lys Ala Lys Gln Arg Ser Cys 200 Gly Leu Val Pro Arg Gly Ṣer Gly Pro Gly Ser Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp 235 Asn Phe Thr Asn Asp Leu Asn Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu Asn Ile Ser Leu Asp Leu Ile Gln Gln 265 260 Tyr Tyr Leu Thr Phe Asn Phe Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile Ile Gly Gln Leu Glu Leu Met Pro Asn 295 Ile Glu Arg Phe Pro Asn Gly Lys Lys Tyr Glu Leu Asp Lys Tyr Thr 315 Met Phe His Tyr Leu Arg Ala Gln Glu Phe Glu His Gly Lys Ser Arg 325 330 Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg 345 Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu Gly Trp Val Glu Gln Leu Val Tyr Asp

375

380





Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp 390 395 Ile Thr Ile Ile Pro Tyr Ile Gly Pro Ala Leu Asn Ile Gly Asn 410 Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala 425 Val Ile Leu Leu Glu Phe Ile Pro Glu Ile Ala Ile Pro Val Leu Gly 440 Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser Lys Arg Asn Glu Lys Trp Asp Glu Val 475 Tyr Lys Tyr Ile Val Thr Asn Trp Leu Ala Lys Val Asn Thr Gln Ile 490 Asp Leu Ile Arg Lys Lys Met Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu 520 Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu 535 Asn Glu Ser Ile Asn Lys Ala Met Ile Asn Ile Asn Lys Phe Leu Asn 550 555 Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu 610 615 620 Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr 630 635 Ile Lys Asn Ile Ile Asn Thr Ser Ile Leu Asn Leu Arg Tyr Glu Ser 645 Asn His Leu Ile Asp Leu Ser Arg Tyr Ala Ser Lys Ile Asn Ile Gly Ser Lys Val Asn Phe Asp Pro Ile Asp Lys Asn Gln Ile Gln Leu Phe 680 675 Asn Leu Glu Ser Ser Lys Ile Glu Val Ile Leu Lys Asn Ala Ile Val Tyr Asn Ser Met Tyr Glu Asn Phe Ser Thr Ser Phe Trp Ile Arg Ile Pro Lys Tyr Phe Asn Ser Ile Ser Leu Asn Asn Glu Tyr Thr Ile Ile 725 730 735





Asn Cys Met Glu Asn Asn Ser Gly Trp Lys Val Ser Leu Asn Tyr Gly 745 Glu Ile Ile Trp Thr Leu Gln Asp Thr Gln Glu Ile Lys Gln Arg Val Val Phe Lys Tyr Ser Gln Met Ile Asn Ile Ser Asp Tyr Ile Asn Arg 775 Trp Ile Phe Val Thr Ile Thr Asn Asn Arg Leu Asn Asn Ser Lys Ile 795 Tyr Ile Asn Gly Arg Leu Ile Asp Gln Lys Pro Ile Ser Asn Leu Gly Asn Ile His Ala Ser Asn Asn Ile Met Phe Lys Leu Asp Gly Cys Arg 825 Asp Thr His Arg Tyr Ile Trp Ile Lys Tyr Phe Asn Leu Phe Asp Lys 840 Glu Leu Asn Glu Lys Glu Ile Lys Asp Leu Tyr Asp Asn Gln Ser Asn Ser Gly Ile Leu Lys Asp Phe Trp Gly Asp Tyr Leu Gln Tyr Asp Lys 870 875 Pro Tyr Tyr Met Leu Asn Leu Tyr Asp Pro Asn Lys Tyr Val Asp Val Asn Asn Val Gly Ile Arg Gly Tyr Met Tyr Leu Lys Gly Pro Arg Gly 905 900 Ser Val Met Thr Thr Asn Ile Tyr Leu Asn Ser Ser Leu Tyr Arg Gly Thr Lys Phe Ile Ile Lys Lys Tyr Ala Ser Gly Asn Lys Asp Asn Ile Val Arg Asn Asn Asp Arg Val Tyr Ile Asn Val Val Lys Asn Lys 955 Glu Tyr Arg Leu Ala Thr Asn Ala Ser Gln Ala Gly Val Glu Lys Ile 965 Leu Ser Ala Leu Glu Ile Pro Asp Val Gly Asn Leu Ser Gln Val Val 985 Val Met Lys Ser Lys Asn Asp Gln Gly Ile Thr Asn Lys Cys Lys Met Asn Leu Gln Asp Asn Asn Gly Asn Asp Ile Gly Phe Ile Gly Phe His 1015 1020 Gln Phe Asn Asn Ile Ala Lys Leu Val Ala Ser Asn Trp Tyr Asn Arg 1030 1035 Gln Ile Glu Arg Ser Ser Arg Thr Leu Gly Cys Ser Trp Glu Phe Ile 1050 Pro Val Asp Asp Gly Trp Gly Glu Arg Pro Leu





<211> 1070

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:construct

<400> 4

Met Pro Phe Glu Leu Pro Ala Leu Pro Tyr Pro Tyr Asp Ala Leu Glu
1 5 10 15

Pro His Ile Asp Lys Glu Thr Met Asn Ile His His Thr Lys His His 20 25 30

Asn Thr Tyr Val Thr Asn Leu Asn Ala Ala Leu Glu Gly His Pro Asp $35 \hspace{1cm} 40 \hspace{1cm} 45$

Leu Gln Asn Lys Ser Leu Glu Glu Leu Leu Ser Asn Leu Glu Ala Leu 50 55 60

Pro Glu Ser Ile Arg Thr Ala Val Arg Asn Asn Gly Gly His Ala 65 70 75 80

Asn His Ser Leu Phe Trp Thr Ile Leu Ser Pro Asn Gly Gly Glu 85 90 95

Pro Thr Gly Glu Leu Ala Asp Ala Ile Asn Lys Lys Phe Gly Ser Phe 100 105 110

Thr Ala Phe Lys Asp Glu Phe Ser Lys Ala Ala Ala Gly Arg Phe Gly 115 120 125

Ser Gly Trp Ala Trp Leu Val Val Asn Asn Gly Glu Leu Glu Ile Thr 130 135 140

Ser Thr Pro Asn Gln Asp Ser Pro Ile Met Glu Gly Lys Thr Pro Ile 145 150 155 160

Leu Gly Leu Asp Val Trp Glu His Ala Tyr Tyr Leu Lys Tyr Gln Asn 165 170 175

Arg Arg Pro Glu Tyr Ile Ala Ala Phe Trp Asn Val Val Asn Trp Asp 180 185 190

Glu Val Ala Lys Arg Tyr Ser Glu Ala Lys Ala Lys Gln Arg Ser Cys 195 200 205

Gly Leu Val Pro Arg Gly Ser Gly Pro Gly Ser Lys Ala Pro Gly Ile

Cys Ile Asp Val Asp Asn Glu Asp Leu Phe Phe Ile Ala Asp Lys Asn 225 230 235 240

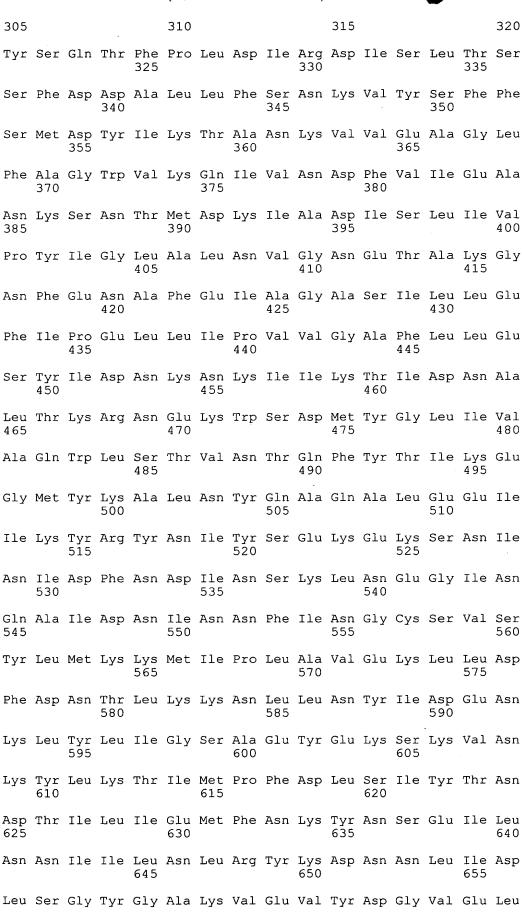
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Gln Ser Asn Tyr Ile Glu Asn Asp Phe Pro Ile Asn Glu Leu Ile Leu 260 265 270

Asp Thr Asp Leu Ile Ser Lys Ile Glu Leu Pro Ser Glu Asn Thr Glu 275 280 285

Ser Leu Thr Asp Phe Asn Val Asp Val Pro Val Tyr Glu Lys Gln Pro 290 295 300

Ala Ile Lys Lys Ile Phe Thr Asp Glu Asn Thr Ile Phe Gln Tyr Leu





4

CC0	CCE	C70
660	665	670

Asn Asp Lys Asn Gln Phe Lys Leu Thr Ser Ser Ala Asn Ser Lys Ile 680 Arg Val Thr Gln Asn Gln Asn Ile Ile Phe Asn Ser Val Phe Leu Asp Phe Ser Val Ser Phe Trp Ile Arg Ile Pro Lys Tyr Lys Asn Asp Gly Ile Gln Asn Tyr Ile His Asn Glu Tyr Thr Ile Ile Asn Cys Met Lys Asn Asn Ser Gly Trp Lys Ile Ser Ile Arg Gly Asn Arg Ile Ile Trp Thr Leu Ile Asp Ile Asn Gly Lys Thr Lys Ser Val Phe Phe Glu Tyr 760 Asn Ile Arg Glu Asp Ile Ser Glu Tyr Ile Asn Arg Trp Phe Phe Val Thr Ile Thr Asn Asn Leu Asn Asn Ala Lys Ile Tyr Ile Asn Gly Lys Leu Glu Ser Asn Thr Asp Ile Lys Asp Ile Arg Glu Val Ile Ala Asn Gly Glu Ile Ile Phe Lys Leu Asp Gly Asp Ile Asp Arg Thr Gln Phe Ile Trp Met Lys Tyr Phe Ser Ile Phe Asn Thr Glu Leu Ser Gln Ser 840 Asn Ile Glu Glu Arg Tyr Lys Ile Gln Ser Tyr Ser Glu Tyr Leu Lys Asp Phe Trp Gly Asn Pro Leu Met Tyr Asn Lys Glu Tyr Tyr Met Phe Asn Ala Gly Asn Lys Asn Ser Tyr Ile Lys Leu Lys Lys Asp Ser Pro 885 Val Gly Glu Ile Leu Thr Arg Ser Lys Tyr Asn Gln Asn Ser Lys Tyr Ile Asn Tyr Arg Asp Leu Tyr Ile Gly Glu Lys Phe Ile Ile Arg Arg 920 Lys Ser Asn Ser Gln Ser Ile Asn Asp Asp Ile Val Arg Lys Glu Asp Tyr Ile Tyr Leu Asp Phe Phe Asn Leu Asn Gln Glu Trp Arg Val Tyr 950 955 Thr Tyr Lys Tyr Phe Lys Lys Glu Glu Lys Leu Phe Leu Ala Pro Ile Ser Asp Ser Asp Glu Phe Tyr Asn Thr Ile Gln Ile Lys Glu Tyr 985 Asp Glu Gln Pro Thr Tyr Ser Cys Gln Leu Leu Phe Lys Lys Asp Glu 1000 Glu Ser Thr Asp Glu Ile Gly Leu Ile Gly Ile His Arg Phe Tyr Glu



1010 1015 1020

Ser Gly Ile Val Phe Glu Glu Tyr Lys Asp Tyr Phe Cys Ile Ser Lys 1025 1030 1035 1040

Trp Tyr Leu Lys Glu Val Lys Arg Lys Pro Tyr Asn Leu Lys Leu Gly 1045 1050 1055

Cys Asn Trp Gln Phe Ile Pro Lys Asp Glu Gly Trp Thr Glu 1060 1065 1070

<210> 5

<211> 1059

<212> PRT

<213> Artificial Sequence

<2205

<223> Description of Artificial Sequence:construct

<400> 5

Met Pro Phe Glu Leu Pro Ala Leu Pro Tyr Pro Tyr Asp Ala Leu Glu 1 5 10 15

Pro His Ile Asp Lys Glu Thr Met Asn Ile His His Thr Lys His His 20 25 30

Asn Thr Tyr Val Thr Asn Leu Asn Ala Ala Leu Glu Gly His Pro Asp 35 40 45

Leu Gln Asn Lys Ser Leu Glu Glu Leu Leu Ser Asn Leu Glu Ala Leu 50 55 60

Pro Glu Ser Ile Arg Thr Ala Val Arg Asn Asn Gly Gly Gly His Ala 65 70 75 80

As His Ser Leu Phe Trp Thr Ile Leu Ser Pro As Gly Gly Glu 85 90 95

Pro Thr Gly Glu Leu Ala Asp Ala Ile Asn Lys Lys Phe Gly Ser Phe 100 105 110

Thr Ala Phe Lys Asp Glu Phe Ser Lys Ala Ala Ala Gly Arg Phe Gly 115 120 125

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Ser Thr Pro Asn Gln Asp Ser Pro Ile Met Glu Gly Lys Thr Pro Ile 145 150 155 160

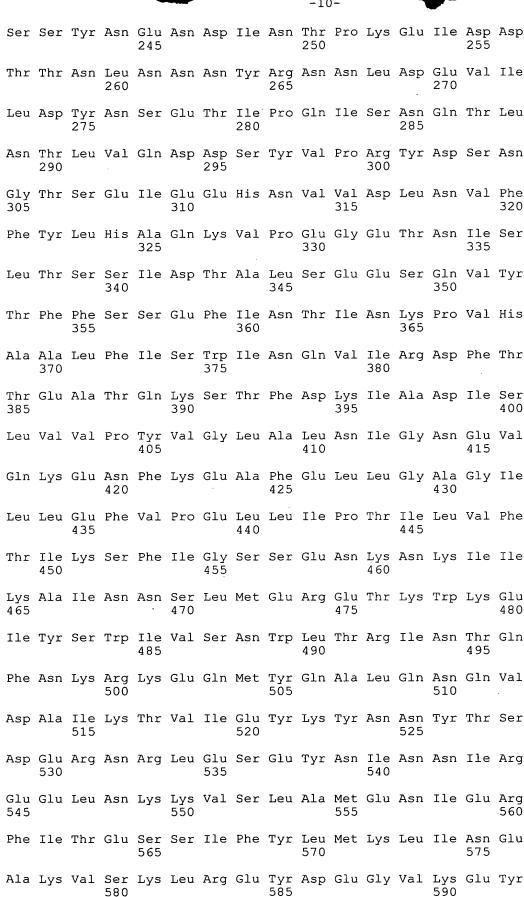
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Arg Arg Pro Glu Tyr Ile Ala Ala Phe Trp Asn Val Val Asn Trp Asp 180. 185 190

Glu Val Ala Lys Arg Tyr Ser Glu Ala Lys Ala Lys Gln Arg Ser Cys 195 200 205

Gly Leu Val Pro Arg Gly Ser Gly Pro Gly Ser Lys Ala Pro Pro Arg 210 215 220

Leu Cys Ile Arg Val Asn Asn Arg Glu Leu Phe Phe.Val Ala Ser Glu 225 230 235 240







Leu Leu Asp Tyr Ile Ser Glu His Arg Ser Ile Leu Gly Asn Ser Val 600 605 Gln Glu Leu Asn Asp Leu Val Thr Ser Thr Leu Asn Asn Ser Ile Pro 615 Phe Glu Leu Ser Ser Tyr Thr Asn Asp Lys Ile Leu Ile Leu Tyr Phe 635 Asn Lys Leu Tyr Lys Lys Ile Lys Asp Asn Ser Ile Leu Asp Met Arg Tyr Glu Asn Asn Lys Phe Ile Asp Ile Ser Gly Tyr Gly Ser Asn Ile Ser Ile Asn Gly Asp Val Tyr Ile Tyr Ser Thr Asn Arg Asn Gln Phe Gly Ile Tyr Ser Ser Lys Pro Ser Glu Val Asn Ile Ala Gln Asn Asn 695 Asp Ile Ile Tyr Asn Gly Arg Tyr Gln Asn Phe Ser Ile Ser Phe Trp Val Arg Ile Pro Lys Tyr Phe Asn Lys Val Asn Leu Asn Asn Glu Tyr 730 Thr Ile Ile Asp Cys Ile Arg Asn Asn Ser Gly Trp Lys Ile Ser Leu Asn Tyr Asn Lys Ile Ile Trp Thr Leu Gln Asp Thr Ala Gly Asn 760 Asn Gln Lys Leu Val Phe Asn Tyr Thr Gln Met Ile Ser Ile Ser Asp Tyr Ile Asn Lys Trp Ile Phe Val Thr Ile Thr Asn Asn Arg Leu Gly 795 Asn Ser Arg Ile Tyr Ile Asn Gly Asn Leu Ile Asp Glu Lys Ser Ile Ser Asn Leu Gly Asp Ile His Val Ser Asp Asn Ile Leu Phe Lys Ile 820 Val Gly Cys Asn Asp Thr Arg Tyr Val Gly Ile Arg Tyr Phe Lys Val Phe Asp Thr Glu Leu Gly Lys Thr Glu Ile Glu Thr Leu Tyr Ser Asp Glu Pro Asp Pro Ser Ile Leu Lys Asp Phe Trp Gly Asn Tyr Leu Leu 870 875 Tyr Asn Lys Arg Tyr Tyr Leu Leu Asn Leu Leu Arg Thr Asp Lys Ser 890 Ile Thr Gln Asn Ser Asn Phe Leu Asn Ile Asn Gln Gln Arg Gly Val 905 Tyr Gln Lys Pro Asn Ile Phe Ser Asn Thr Arg Leu Tyr Thr Gly Val Glu Val Ile Ile Arg Lys Asn Gly Ser Thr Asp Ile Ser Asn Thr Asp 940 935



Asn Phe Val Arg Lys Asn Asp Leu Ala Tyr Ile Asn Val Val Asp Arg 945 950 955 960

Asp Val Glu Tyr Arg Leu Tyr Ala Asp Ile Ser Ile Ala Lys Pro Glu 965 970 975

Lys Ile Ile Lys Leu Ile Arg Thr Ser Asn Ser Asn Ser Leu Gly 980 985 990

Gln Ile Ile Val Met Asp Ser Ile Gly Asn Asn Cys Thr Met Asn Phe 995 1000 1005

Gln Asn Asn Gly Gly Asn Ile Gly Leu Leu Gly Phe His Ser Asn 1010 1015 1020

Asn Leu Val Ala Ser Ser Trp Tyr Tyr Asn Asn Ile Arg Lys Asn Thr 1025 1030 1035 1040

Ser Ser Asn Gly Cys Phe Trp Ser Phe Ile Ser Lys Glu His Gly Trp \$1045\$ \$1050\$ \$1055\$

Gln Glu Asn

<210> 6

<211> 1092

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:construct

<400> 6

Met Leu Ser Arg Ala Val Cys Gly Thr Ser Arg Gln Leu Ala Pro Ala 1 5 10 15

Leu Gly Tyr Leu Gly Ser Arg Gln Lys His Ser Arg Gly Ser Pro Ala 20 25 30

Leu Pro Tyr Pro Tyr Asp Ala Leu Glu Pro His Ile Asp Lys Glu Thr 35 40 45

Met Asn Ile His His Thr Lys His His Asn Thr Tyr Val Thr Asn Leu
50 60

Asn Ala Ala Leu Glu Gly His Pro Asp Leu Gln Asn Lys Ser Leu Glu 65 70 75 80

Glu Leu Leu Ser Asn Leu Glu Ala Leu Pro Glu Ser Ile Arg Thr Ala 85 90 95

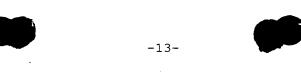
Val Arg Asn Asn Gly Gly Gly His Ala Asn His Ser Leu Phe Trp Thr 100 105 110

Ile Leu Ser Pro Asn Gly Gly Glu Pro Thr Gly Glu Leu Ala Asp 115 120 125

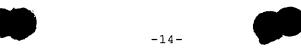
Ala Ile Asn Lys Lys Phe Gly Ser Phe Thr Ala Phe Lys Asp Glu Phe 130 140

Ser Lys Ala Ala Ala Gly Arg Phe Gly Ser Gly Trp Ala Trp Leu Val 145 150 155 160

Val Asn Asn Gly Glu Leu Glu Ile Thr Ser Thr Pro Asn Gln Asp Ser



165 170 175 Pro Ile Met Glu Gly Lys Thr Pro Ile Leu Gly Leu Asp Val Trp Glu 185 His Ala Tyr Tyr Leu Lys Tyr Gln Asn Arg Arg Pro Glu Tyr Ile Ala Ala Phe Trp Asn Val Val Asn Trp Asp Glu Val Ala Lys Arg Tyr Ser 215 Glu Ala Lys Ala Lys Gln Arg Ser Cys Gly Leu Val Pro Arg Gly Ser Gly Pro Gly Ser Ala Leu Asn Asp Leu Cys Ile Lys Val Asn Asn Trp Asp Leu Phe Phe Ser Pro Ser Glu Asp Asn Phe Thr Asn Asp Leu Asn 260 265 Lys Gly Glu Glu Ile Thr Ser Asp Thr Asn Ile Glu Ala Ala Glu Glu 280 Asn Ile Ser Leu Asp Leu Ile Gln Gln Tyr Tyr Leu Thr Phe Asn Phe 295 Asp Asn Glu Pro Glu Asn Ile Ser Ile Glu Asn Leu Ser Ser Asp Ile 310 315 Ile Gly Gln Leu Glu Leu Met Pro Asn Ile Glu Arg Phe Pro Asn Gly 325 Lys Lys Tyr Glu Leu Asp Lys Tyr Thr Met Phe His Tyr Leu Arg Ala 345 Gln Glu Phe Glu His Gly Lys Ser Arg Ile Ala Leu Thr Asn Ser Val Asn Glu Ala Leu Leu Asn Pro Ser Arg Val Tyr Thr Phe Phe Ser Ser Asp Tyr Val Lys Lys Val Asn Lys Ala Thr Glu Ala Ala Met Phe Leu 390 395 Gly Trp Val Glu Gln Leu Val Tyr Asp Phe Thr Asp Glu Thr Ser Glu Val Ser Thr Thr Asp Lys Ile Ala Asp Ile Thr Ile Ile Ile Pro Tyr 425 Ile Gly Pro Ala Leu Asn Ile Gly Asn Met Leu Tyr Lys Asp Asp Phe Val Gly Ala Leu Ile Phe Ser Gly Ala Val Ile Leu Leu Glu Phe Ile 455 460 Pro Glu Ile Ala Ile Pro Val Leu Gly Thr Phe Ala Leu Val Ser Tyr Ile Ala Asn Lys Val Leu Thr Val Gln Thr Ile Asp Asn Ala Leu Ser 490 Lys Arg Asn Glu Lys Trp Asp Glu Val Tyr Lys Tyr Ile Val Thr Asn 500 505 Trp Leu Ala Lys Val Asn Thr Gln Ile Asp Leu Ile Arg Lys Lys Met



515 520 525 Lys Glu Ala Leu Glu Asn Gln Ala Glu Ala Thr Lys Ala Ile Ile Asn 535 Tyr Gln Tyr Asn Gln Tyr Thr Glu Glu Glu Lys Asn Asn Ile Asn Phe Asn Ile Asp Asp Leu Ser Ser Lys Leu Asn Glu Ser Ile Asn Lys Ala 565 Met Ile Asn Ile Asn Lys Phe Leu Asn Gln Cys Ser Val Ser Tyr Leu Met Asn Ser Met Ile Pro Tyr Gly Val Lys Arg Leu Glu Asp Phe Asp Ala Ser Leu Lys Asp Ala Leu Leu Lys Tyr Ile Tyr Asp Asn Arg Gly Thr Leu Ile Gly Gln Val Asp Arg Leu Lys Asp Lys Val Asn Asn Thr Leu Ser Thr Asp Ile Pro Phe Gln Leu Ser Lys Tyr Val Asp Asn Gln Arg Leu Leu Ser Thr Phe Thr Glu Tyr Ile Lys Asn Ile Ile Asn Thr 665 Ser Ile Leu Asn Leu Arg Tyr Glu Ser Asn His Leu Ile Asp Leu Ser Arg Tyr Ala Ser Lys Ile Asn Ile Gly Ser Lys Val Asn Phe Asp Pro 695 Ile Asp Lys Asn Gln Ile Gln Leu Phe Asn Leu Glu Ser Ser Lys Ile 710 Glu Val Ile Leu Lys Asn Ala Ile Val Tyr Asn Ser Met Tyr Glu Asn Phe Ser Thr Ser Phe Trp Ile Arg Ile Pro Lys Tyr Phe Asn Ser Ile 740 745 Ser Leu Asn Asn Glu Tyr Thr Ile Ile Asn Cys Met Glu Asn Asn Ser Gly Trp Lys Val Ser Leu Asn Tyr Gly Glu Ile Ile Trp Thr Leu Gln 775 Asp Thr Gln Glu Ile Lys Gln Arg Val Val Phe Lys Tyr Ser Gln Met Ile Asn Ile Ser Asp Tyr Ile Asn Arg Trp Ile Phe Val Thr Ile Thr 810 Asn Asn Arg Leu Asn Asn Ser Lys Ile Tyr Ile Asn Gly Arg Leu Ile Asp Gln Lys Pro Ile Ser Asn Leu Gly Asn Ile His Ala Ser Asn Asn Ile Met Phe Lys Leu Asp Gly Cys Arg Asp Thr His Arg Tyr Ile Trp 855 Ile Lys Tyr Phe Asn Leu Phe Asp Lys Glu Leu Asn Glu Lys Glu Ile



870 875 880 865 Lys Asp Leu Tyr Asp Asn Gln Ser Asn Ser Gly Ile Leu Lys Asp Phe 885 Trp Gly Asp Tyr Leu Gln Tyr Asp Lys Pro Tyr Tyr Met Leu Asn Leu Tyr Asp Pro Asn Lys Tyr Val Asp Val Asn Asn Val Gly Ile Arg Gly 920 Tyr Met Tyr Leu Lys Gly Pro Arg Gly Ser Val Met Thr Thr Asn Ile Tyr Leu Asn Ser Ser Leu Tyr Arg Gly Thr Lys Phe Ile Ile Lys Lys Tyr Ala Ser Gly Asn Lys Asp Asn Ile Val Arg Asn Asn Asp Arg Val Tyr Ile Asn Val Val Lys Asn Lys Glu Tyr Arg Leu Ala Thr Asn 985 Ala Ser Gln Ala Gly Val Glu Lys Ile Leu Ser Ala Leu Glu Ile Pro Asp Val Gly Asn Leu Ser Gln Val Val Wat Lys Ser Lys Asn Asp 1015 1020 Gln Gly Ile Thr Asn Lys Cys Lys Met Asn Leu Gln Asp Asn Asn Gly 1035 Asn Asp Ile Gly Phe Ile Gly Phe His Gln Phe Asn Asn Ile Ala Lys 1045 1050 Leu Val Ala Ser Asn Trp Tyr Asn Arg Gln Ile Glu Arg Ser Ser Arg 1065 Thr Leu Gly Cys Ser Trp Glu Phe Ile Pro Val Asp Asp Gly Trp Gly 1080 Glu Arg Pro Leu 1090 <210> 7 <213> Artificial Sequence

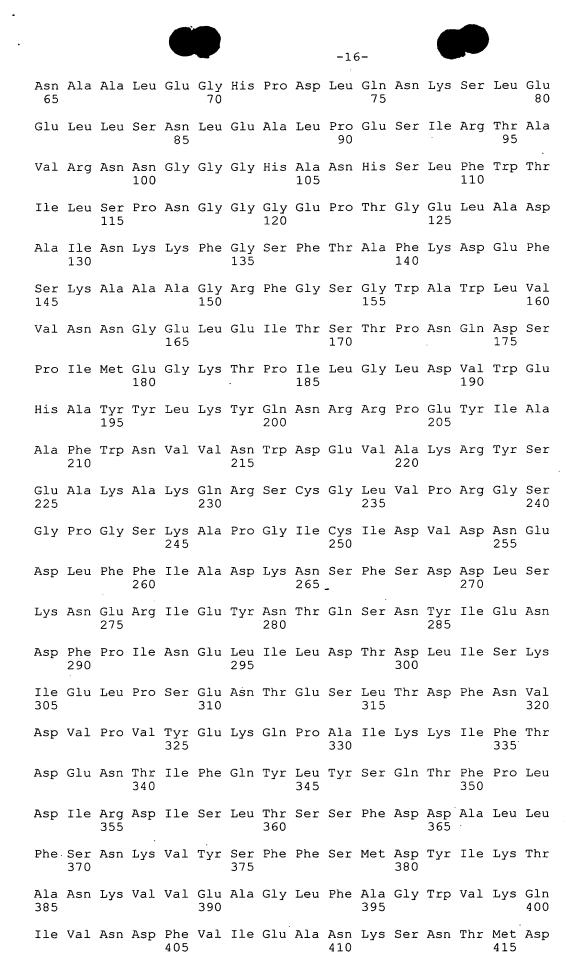
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<223> Description of Artificial Sequence:construct

55

Met Leu Ser Arg Ala Val Cys Gly Thr Ser Arg Gln Leu Ala Pro Ala Leu Gly Tyr Leu Gly Ser Arg Gln Lys His Ser Arg Gly Ser Pro Ala Leu Pro Tyr Pro Tyr Asp Ala Leu Glu Pro His Ile Asp Lys Glu Thr Met Asn Ile His His Thr Lys His His Asn Thr Tyr Val Thr Asn Leu

60



•





Lys Ile Ala Asp Ile Ser Leu Ile Val Pro Tyr Ile Gly Leu Ala Leu 425 Asn Val Gly Asn Glu Thr Ala Lys Gly Asn Phe Glu Asn Ala Phe Glu Ile Ala Gly Ala Ser Ile Leu Leu Glu Phe Ile Pro Glu Leu Leu Ile 455 Pro Val Val Gly Ala Phe Leu Leu Glu Ser Tyr Ile Asp Asn Lys Asn 470 475 Lys Ile Ile Lys Thr Ile Asp Asn Ala Leu Thr Lys Arg Asn Glu Lys Trp Ser Asp Met Tyr Gly Leu Ile Val Ala Gln Trp Leu Ser Thr Val Asn Thr Gln Phe Tyr Thr Ile Lys Glu Gly Met Tyr Lys Ala Leu Asn 520 Tyr Gln Ala Gln Ala Leu Glu Glu Ile Ile Lys Tyr Arg Tyr Asn Ile 535 Tyr Ser Glu Lys Glu Lys Ser Asn Ile Asn Ile Asp Phe Asn Asp Ile 550 555 Asn Ser Lys Leu Asn Glu Gly Ile Asn Gln Ala Ile Asp Asn Ile Asn 570 · Asn Phe Ile Asn Gly Cys Ser Val Ser Tyr Leu Met Lys Lys Met Ile 585 580 Pro Leu Ala Val Glu Lys Leu Leu Asp Phe Asp Asn Thr Leu Lys Lys Asn Leu Leu Asn Tyr Ile Asp Glu Asn Lys Leu Tyr Leu Ile Gly Ser 615 Ala Glu Tyr Glu Lys Ser Lys Val Asn Lys Tyr Leu Lys Thr Ile Met Pro Phe Asp Leu Ser Ile Tyr Thr Asn Asp Thr Ile Leu Ile Glu Met 645 650 Phe Asn Lys Tyr Asn Ser Glu Ile Leu Asn Asn Ile Ile Leu Asn Leu 665 Arg Tyr Lys Asp Asn Asn Leu Ile Asp Leu Ser Gly Tyr Gly Ala Lys Val Glu Val Tyr Asp Gly Val Glu Leu Asn Asp Lys Asn Gln Phe Lys 695 Leu Thr Ser Ser Ala Asn Ser Lys Ile Arg Val Thr Gln Asn Gln Asn Ile Ile Phe Asn Ser Val Phe Leu Asp Phe Ser Val Ser Phe Trp Ile Arg Ile Pro Lys Tyr Lys Asn Asp Gly Ile Gln Asn Tyr Ile His Asn Glu Tyr Thr Ile Ile Asn Cys Met Lys Asn Asn Ser Gly Trp Lys Ile

760



Ser Ile Arg Gly Asn Arg Ile Ile Trp Thr Leu Ile Asp Ile Asn Gly 775 780 Lys Thr Lys Ser Val Phe Phe Glu Tyr Asn Ile Arg Glu Asp Ile Ser 795 Glu Tyr Ile Asn Arg Trp Phe Phe Val Thr Ile Thr Asn Asn Leu Asn Asn Ala Lys Ile Tyr Ile Asn Gly Lys Leu Glu Ser Asn Thr Asp Ile 825 Lys Asp Ile Arg Glu Val Ile Ala Asn Gly Glu Ile Ile Phe Lys Leu Asp Gly Asp Ile Asp Arg Thr Gln Phe Ile Trp Met Lys Tyr Phe Ser 855 Ile Phe Asn Thr Glu Leu Ser Gln Ser Asn Ile Glu Glu Arg Tyr Lys 870 875 880 Ile Gln Ser Tyr Ser Glu Tyr Leu Lys Asp Phe Trp Gly Asn Pro Leu Met Tyr Asn Lys Glu Tyr Tyr Met Phe Asn Ala Gly Asn Lys Asn Ser 905 Tyr Ile Lys Leu Lys Lys Asp Ser Pro Val Gly Glu Ile Leu Thr Arg Ser Lys Tyr Asn Gln Asn Ser Lys Tyr Ile Asn Tyr Arg Asp Leu Tyr 935 Ile Gly Glu Lys Phe Ile Ile Arg Arg Lys Ser Asn Ser Gln Ser Ile Asn Asp Asp Ile Val Arg Lys Glu Asp Tyr Ile Tyr Leu Asp Phe Phe Asn Leu Asn Gln Glu Trp Arg Val Tyr Thr Tyr Lys Tyr Phe Lys Lys Glu Glu Lys Leu Phe Leu Ala Pro Ile Ser Asp Ser Asp Glu Phe 1000 Tyr Asn Thr Ile Gln Ile Lys Glu Tyr Asp Glu Gln Pro Thr Tyr Ser Cys Gln Leu Leu Phe Lys Lys Asp Glu Glu Ser Thr Asp Glu Ile Gly 1025 Leu Ile Gly Ile His Arg Phe Tyr Glu Ser Gly Ile Val Phe Glu Glu 1045 1050 Tyr Lys Asp Tyr Phe Cys Ile Ser Lys Trp Tyr Leu Lys Glu Val Lys 1065 1060 Arg Lys Pro Tyr Asn Leu Lys Leu Gly Cys Asn Trp Gln Phe Ile Pro 1080 Lys Asp Glu Gly Trp Thr Glu

<210> 8





<211> 1084

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:construct

<400> 8

Met Leu Ser Arg Ala Val Cys Gly Thr Ser Arg Gln Leu Ala Pro Ala 1 5 10 15

Leu Gly Tyr Leu Gly Ser Arg Gln Lys His Ser Arg Gly Ser Pro Ala 20 25 30

Leu Pro Tyr Pro Tyr Asp Ala Leu Glu Pro His Ile Asp Lys Glu Thr 35 40 45

Met Asn Ile His His Thr Lys His His Asn Thr Tyr Val Thr Asn Leu 50 60

Asn Ala Ala Leu Glu Gly His Pro Asp Leu Gln Asn Lys Ser Leu Glu 65 70 75 80

Glu Leu Leu Ser Asn Leu Glu Ala Leu Pro Glu Ser Ile Arg Thr Ala 85 90 95

Val Arg Asn Asn Gly Gly Gly His Ala Asn His Ser Leu Phe Trp Thr 100 105 110

Ile Leu Ser Pro Asn Gly Gly Glu Pro Thr Gly Glu Leu Ala Asp 115 120 125

Ala Ile Asn Lys Lys Phe Gly Ser Phe Thr Ala Phe Lys Asp Glu Phe 130 135 140

Ser Lys Ala Ala Ala Gly Arg Phe Gly Ser Gly Trp Ala Trp Leu Val 145 150 155 160

Val Asn Asn Gly Glu Leu Glu Ile Thr Ser Thr Pro Asn Gln Asp Ser 165 170 175

Pro Ile Met Glu Gly Lys Thr Pro Ile Leu Gly Leu Asp Val Trp Glu 180 185 190

His Ala Tyr Tyr Leu Lys Tyr Gln Asn Arg Arg Pro Glu Tyr Ile Ala 195 200 205

Ala Phe Trp Asn Val Val Asn Trp Asp Glu Val Ala Lys Arg Tyr Ser 210 215 220

Glu Ala Lys Ala Lys Gln Arg Ser Cys Gly Leu Val Pro Arg Gly Ser 225 230 235 240

Gly Pro Gly Ser Lys Ala Pro Pro Arg Leu Cys Ile Arg Val Asn Asn 245 250 255

Arg Glu Leu Phe Phe Val Ala Ser Glu Ser Ser Tyr Asn Glu Asn Asp 260 265 270

Ile Asn Thr Pro Lys Glu Ile Asp Asp Thr Thr Asn Leu Asn Asn 275 280 285

Tyr Arg Asn Asn Leu Asp Glu Val Ile Leu Asp Tyr Asn Ser Glu Thr 290 295 300

Ile Pro Gln Ile Ser Asn Gln Thr Leu Asn Thr Leu Val Gln Asp Asp

-20-315 320 Ser Tyr Val Pro Arg Tyr Asp Ser Asn Gly Thr Ser Glu Ile Glu Glu 330 His Asn Val Val Asp Leu Asn Val Phe Phe Tyr Leu His Ala Gln Lys Val Pro Glu Gly Glu Thr Asn Ile Ser Leu Thr Ser Ser Ile Asp Thr 360 410 475 490

Ala Leu Ser Glu Glu Ser Gln Val Tyr Thr Phe Phe Ser Ser Glu Phe Ile Asn Thr Ile Asn Lys Pro Val His Ala Ala Leu Phe Ile Ser Trp Ile Asn Gln Val Ile Arg Asp Phe Thr Thr Glu Ala Thr Gln Lys Ser Thr Phe Asp Lys Ile Ala Asp Ile Ser Leu Val Val Pro Tyr Val Gly Leu Ala Leu Asn Ile Gly Asn Glu Val Gln Lys Glu Asn Phe Lys Glu Ala Phe Glu Leu Leu Gly Ala Gly Ile Leu Leu Glu Phe Val Pro Glu Leu Leu Ile Pro Thr Ile Leu Val Phe Thr Ile Lys Ser Phe Ile Gly Ser Ser Glu Asn Lys Asn Lys Ile Ile Lys Ala Ile Asn Asn Ser Leu Met Glu Arg Glu Thr Lys Trp Lys Glu Ile Tyr Ser Trp Ile Val Ser Asn Trp Leu Thr Arg Ile Asn Thr Gln Phe Asn Lys Arg Lys Glu Gln Met Tyr Gln Ala Leu Gln Asn Gln Val Asp Ala Ile Lys Thr Val Ile Glu Tyr Lys Tyr Asn Asn Tyr Thr Ser Asp Glu Arg Asn Arg Leu Glu Ser Glu Tyr Asn Ile Asn Asn Ile Arg Glu Glu Leu Asn Lys Lys Val Ser Leu Ala Met Glu Asn Ile Glu Arg Phe Ile Thr Glu Ser Ser Ile Phe Tyr Leu Met Lys Leu Ile Asn Glu Ala Lys Val Ser Lys Leu Arg 600 Glu Tyr Asp Glu Gly Val Lys Glu Tyr Leu Leu Asp Tyr Ile Ser Glu His Arg Ser Ile Leu Gly Asn Ser Val Gln Glu Leu Asn Asp Leu Val 635 Thr Ser Thr Leu Asn Asn Ser Ile Pro Phe Glu Leu Ser Ser Tyr Thr Asn Asp Lys Ile Leu Ile Leu Tyr Phe Asn Lys Leu Tyr Lys Lys Ile

305





660 665 670

Lys Asp Asn Ser Ile Leu Asp Met Arg Tyr Glu Asn Asn Lys Phe Ile 680 Asp Ile Ser Gly Tyr Gly Ser Asn Ile Ser Ile Asn Gly Asp Val Tyr Ile Tyr Ser Thr Asn Arg Asn Gln Phe Gly Ile Tyr Ser Ser Lys Pro 715 710 Ser Glu Val Asn Ile Ala Gln Asn Asn Asp Ile Ile Tyr Asn Gly Arg Tyr Gln Asn Phe Ser Ile Ser Phe Trp Val Arg Ile Pro Lys Tyr Phe Asn Lys Val Asn Leu Asn Asn Glu Tyr Thr Ile Ile Asp Cys Ile Arg 765 Asn Asn Asn Ser Gly Trp Lys Ile Ser Leu Asn Tyr Asn Lys Ile Ile Trp Thr Leu Gln Asp Thr Ala Gly Asn Asn Gln Lys Leu Val Phe Asn Tyr Thr Gln Met Ile Ser Ile Ser Asp Tyr Ile Asn Lys Trp Ile Phe 810 805 Val Thr Ile Thr Asn Asn Arg Leu Gly Asn Ser Arg Ile Tyr Ile Asn 825 Gly Asn Leu Ile Asp Glu Lys Ser Ile Ser Asn Leu Gly Asp Ile His Val Ser Asp Asn Ile Leu Phe Lys Ile Val Gly Cys Asn Asp Thr Arg , 855 Tyr Val Gly Ile Arg Tyr Phe Lys Val Phe Asp Thr Glu Leu Gly Lys Thr Glu Ile Glu Thr Leu Tyr Ser Asp Glu Pro Asp Pro Ser Ile Leu 890 885 Lys Asp Phe Trp Gly Asn Tyr Leu Leu Tyr Asn Lys Arg Tyr Tyr Leu Leu Asn Leu Leu Arg Thr Asp Lys Ser Ile Thr Gln Asn Ser Asn Phe 920 Leu Asn Ile Asn Gln Gln Arg Gly Val Tyr Gln Lys Pro Asn Ile Phe Ser Asn Thr Arg Leu Tyr Thr Gly Val Glu Val Ile Ile Arg Lys Asn 950 955 Gly Ser Thr Asp Ile Ser Asn Thr Asp Asn Phe Val Arg Lys Asn Asp Leu Ala Tyr Ile Asn Val Val Asp Arg Asp Val Glu Tyr Arg Leu Tyr Ala Asp Ile Ser Ile Ala Lys Pro Glu Lys Ile Ile Lys Leu Ile Arg 1000 1005 Thr Ser Asn Ser Asn Ser Leu Gly Gln Ile Ile Val Met Asp Ser

1020

1010 1015

Ile Gly Asn Asn Cys Thr Met Asn Phe Gln Asn Asn Asn Gly Gly Asn 1025 1030 1035 1040

Ile Gly Leu Leu Gly Phe His Ser Asn Asn Leu Val Ala Ser Ser Trp 1045 1050 1055

Tyr Tyr Asn Asn Ile Arg Lys Asn Thr Ser Ser Asn Gly Cys Phe Trp 1060 1065 1070

Ser Phe Ile Ser Lys Glu His Gly Trp Gln Glu Asn 1075 1080

<210> 9

<211> 229

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: polypeptide
 comprising a mitochondrial leader from human MnSOD
 and B. Stearothermophilus SOS

<400> 9

Leu Gly Tyr Leu Gly Ser Arg Gln Lys His Ser Arg Gly Ser Pro Ala 20 25 30

Leu Pro Tyr Pro Tyr Asp Ala Leu Glu Pro His Ile Asp Lys Glu Thr 35 40 45

Met Asn Ile His His Thr Lys His His Asn Thr Tyr Val Thr Asn Leu 50 55 60

Asn Ala Ala Leu Glu Gly His Pro Asp Leu Gln Asn Lys Ser Leu Glu 65 .70 .75 80

Glu Leu Leu Ser Asn Leu Glu Ala Leu Pro Glu Ser Ile Arg Thr Ala 85 90 95

Val Arg Asn Asn Gly Gly Gly His Ala Asn His Ser Leu Phe Trp Thr 100 105 110

Ile Leu Ser Pro Asn Gly Gly Glu Pro Thr Gly Glu Leu Ala Asp 115 120 125

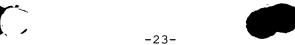
Ala Ile Asn Lys Lys Phe Gly Ser Phe Thr Ala Phe Lys Asp Glu Phe 130 135 140

Ser Lys Ala Ala Ala Gly Arg Phe Gly Ser Gly Trp Ala Trp Leu Val 145 150 155 160

Val Asn Asn Gly Glu Leu Glu Ile Thr Ser Thr Pro Asn Gln Asp Ser 165 170 175

Pro Ile Met Glu Gly Lys Thr Pro Ile Leu Gly Leu Asp Val Trp Glu 180 185 190

His Ala Tyr Tyr Leu Lys Tyr Gln Asn Arg Arg Pro Glu Tyr Ile Ala 195 200 205



Ala Phe Trp Asn Val Val Asn Trp Asp Glu Val Ala Lys Arg Tyr Ser 210 215 220

Glu Ala Lys Ala Lys 225

<210> 10

<211> 24 <212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: modified human mitocondrial leader sequence

<400> 10

Met Leu Ser Arg Ala Val Ser Gly Thr Ser Arg Gln Leu Ala Pro Ala 1 5 10 15

Leu Gly Tyr Leu Gly Ser Arg Gln 20

<210> 11

<211> 24

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: modified human mitochondrial leader sequence

<400> 11

Met Leu Ser Arg Ala Val Cys Gly Thr Ser Arg Gln Leu Ala Pro Ala 1 5 10 15

Leu Gly Tyr Leu Gly Ser Arg Gln 20